SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,831	08/07/2001	Valerie Martelange	L0461/7118 (JRV)	1799

23628 7590 06/30/2004

WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,831	MARTELANGE ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 August 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28 and 44-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28 and 44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/7/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 25-28 and newly added claims 44-50 are pending in the instant application. Claims 1-24 and 29-43 have been canceled in a preliminary amendment.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-28 and 44-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These

factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to diagnosing any disorder by contacting any biological sample from any subject, including non human subjects, with an agent that selectively binds with a tumor associated nucleic acid molecule wherein the tumor associated nucleic acid hybridizes to SEQ ID NO: 42 under specified stringent conditions and determining the expression of the tumor associated nucleic acid molecule wherein expression is diagnostic for the disorder. The claims are further broadly drawn to conditions wherein the agent is a nucleic acid molecule comprising a molecule comprising a nucleotide sequence set forth as SEQ ID NO: 42, fragments thereof, and complements thereof. The claims are also broadly drawn to embodiments wherein the biological sample is non testis tissue (claim 28), to specific methods of detection (claims 44-48), to the disorder being any cancer (claim 49), as well as to specific types of cancer (claim 50). It is clear from the claim recitation that the invention is broadly drawn to diagnosing any disorder based on hybridization of an agent to an agent that hybridizes to SEQ ID NO: 42. It is noted, however, that an agent that hybridizes to a nucleic acid that hybridizes to SEQ ID NO: 42 need not actually hybridize to SEQ ID NO: 42. In other

words, the claims intend that diagnosis is not dependent on identification of SEQ ID NO: 42 or even any fragment or complement of SEQ ID NO: 42.

The amount of direction or guidance, and the presence and absence of working examples:

The specification teaches that an sdp3.8 clone (SEQ ID NO: 1) was identified through subtraction of a sarcoma cell line with sequences from normal uterus, breast, colon, and heart (see page 47). The specification teaches that expression analysis of SEQ ID NO: 1 using RT-PCR analysis showed that it was predominantly expressed in only normal testis tissue and not in a panel of other normal tissue (see page 48-49, and table II). As will be made clear below, it is important to note that the specification does not teach analysis of normal pancreas, and that at the time the invention was filed, the specification teaches that the only normal tissue that RT-PCR analysis of SEQ ID NO: 1 showed expression for was testis tissue. The specification does not contemplate or suggest analysis of biological samples that are non-testis, non pancreatic tissue. The specification teaches that SEQ ID NO: 1 "shares an expression pattern with other tumor associated genes in that it is expressed only in immune privileged normal tissues such as testis" (page 49). The specification teaches that among tumoral samples, SEQ ID NO 1 is expressed in sarcomas (32%), and expressed less frequently in epidermoid carcinomas (10%), non small cell lung carcinoma (7%), and head and neck carcinoma (5%) (page 49, table III). The specification further teaches that the full length clone of SEQ ID NO: 1 was isolated (SEQ ID NO: 42) and found to have homology to p68 RNA helicase and termed HAGE. However, for the reasons set forth below, the specification has not

enabled the skilled artisan to practice the invention commensurate in scope with the claims.

As stated above the claims encompass diagnosis by detecting an agent that binds, ie, for example by hybridization, with a nucleic acid that hybridizes to SEQ ID NO: 42. As SEQ ID NO: 42 was found to have homology to DEAD box helicase, which are known in the art to contain conserved regions, the claims encompass conditions wherein any DEAD box helicase, or any helicase in general would be detected. However, the specification has provided no teaching or working example that expression of any homologue or related sequence of SEQ ID NO: 42, or any helicase, is predictably correlative of the diagnosis of any disorder, or any specific or general cancer. Further, any fragment or any complement of SEQ ID NO: 42, would not be expected to provide expression analysis of SEQ ID NO: 42 alone. While the specification contemplates "unique" sequences, the specification has provided no teaching as to what sequences within SEQ ID NO: 42 make it unique from sequences already known in the art at the time the application was filed or from sequences yet to be determined. Additionally, the specification provides no teaching or working examples that detecting expression of SEQ ID NO: 42 in any non human animal would be diagnostic of any disorder, cancer in general, or any specific forms of cancer. The specification also does not provide any teaching or working examples that expression of variants or homologs of SEQ ID NO: 42 from other species, would be diagnostic of any disorder, cancer in general, or any specific form of cancer.

The state of the prior art and the predictability or unpredictability of the art:

Firstly, it is noted that the claims are drawn to diagnosis based on the binding of any agent to a nucleic acid that hybridizes to SEQ ID NO: 42. This encompasses detection *using* any fragment or complement of SEQ ID NO: 42, SEQ ID NO: 42 itself, as well as detection of variants and homologs of SEQ ID NO: 42, from any source. As noted above, the specification provides no teaching or working examples of such broad reaching diagnosis. The specification only shows that RT-PCR analysis with primers to SEQ ID NO: 1 was found to indicate expression of SEQ ID NO: 1 in testis tissue as well as a few specific forms of cancer. Martelange et al (hereinafter referred to as Martelange, Cancer Research, vol. 60, pages 3848-3855, 2000) teach that HAGE (SEQ ID NO: 42) was found to have homology to members of the DEAD box family of helicases. Martelange specifically teaches that a 2.3 kb HAGE probe was analyzed using Southern hybridization and that it was found to hybridize to other fragments of human genomic DNA (see page 3852, col. 2, 5th paragraph). Martelange teaches that the probe probably hybridized with other members of the DEAD box family because their sequences are well conserved. Therefore, it is clear from the teachings of Martelange that hybridization can lead to false positive results. Because SEQ ID NO: 42 belongs to a class of helicases that have sequences that are well conserved, it would be expected that fragments, complements, and the full sequence would hybridize to other helicases that would be expected to be expressed in other cell types, including non cancerous tissue specimens. As the specification provides not teaching or working examples of such broad ranging diagnosis, or that detection of expression of DEAD box helicases is predictably diagnostic of any disorder, cancer in general, or any specific form of cancer, the scope of the claims allows for a large amount of false positive results. As such, the scope of the

claims does not bear reasonable correlation to the scope of enablement by the provided by the specification. As determined in In re Fisher, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art".

Additionally, the claims encompass diagnosis of any disorder or any cancer, however the post filing date art makes clear that a correlation between diagnosis of specific cancers or any cancer and expression of CT (cancer/testis) antigens (a class of molecules that HAGE is a member of) is unpredictable. Scanlan, et al (hereinafter referred to as Scanlan I, Immunological reviews, vol. 188, pages 22-32, 2002) teaches that expression frequency of individual CT antigens is variable in different tumor types, for example that melanoma generally appears to have the highest frequency (page 24, col. 2, last para), and that the frequency of different CT antigen expression in a single tumor type is highly variable (page 25, col. 1). At the time the invention was filed, the specification only taught expression in a few different cancers, among them: sarcoma, non small cell lung carcinoma, epidermoid carcinoma and head and neck cancer. The specification also teaches that 25 leukemic samples (see table III) showed no expression, however, the post filing date art shows that HAGE is expressed in chronic myeloid leukemias and to a lesser extent in acute myeloid leukemia, see Adams et al (hereinafter referred to as Adams, Leukemia, vol. 16, pages 2238-2242, 2002). The teachings in the specification, however, did not establish a predictable correlation that SEQ ID NO: 1 expression would be found in myeloid leukemias. It is also noted that the claims encompass diagnosis of any type of lung cancer, however SEQ ID NO: 1 was only found to be expressed in non small cell lung cancer (NSCLC). Neither the specification nor the

art provide any predictable correlation that expression of a transcript which is diagnostic of NSCLC, is diagnostic of any type of lung cancer. Further, Scanlan et al (hereinafter referred to as Scanlan II; Cancer Immunity; vol. 4, pages 1-15, 2004) only teaches mRNA expression of HAGE in NSCLC (see Table 3). Additionally, Scanlan II teaches mRNA expression in colon cancer, esophogeal cancer, and renal cancer, whereas the specification teaches finding no expression in 19 colorectal carcinoma samples, 14 esophageal carcinoma samples and 16 renal tumors.

Further, the claims encompass detection in any sample, or any non testis sample. However, the post filing date art teaches of the unpredictability of expression of CT transcript in general, and HAGE specifically, in normal tissues. Scanlan II teaches that HAGE is also expressed in normal pancreas (see page 8). Scanlan II also teaches that there was frequent detection of CT transcripts in normal pancreas and that such was unexpected. Therefore, the post filing date art exemplifies the unpredictability with regard to CT antigen expression in general, and HAGE expression, specifically, in normal tissues. At the time the invention was filed, the specification teaches that SEQ ID NO: 1 was only found to be expressed in normal testis, but no other normal tissues. However, as exemplified by the teachings in the post filing date art, given the teachings in the specification and the knowledge in the art at the time the invention was filed, the skilled artisan would be unable able to predictably diagnose a patient with cancer if a pancreatic tissue sample were provided for analysis of HAGE expression.

A thorough review of the prior art revealed that the state of the prior art at the time of the invention was such that given the teachings in the specification, the skilled artisan would not have able to establish a predictable correlation between the expression

of HAGE, or any fragment, variant, homolog, or complement and diagnosis of any disorder, cancer in general, or any specific type of cancer other than sarcoma, head and neck cancer, NSCLC, and epidermoid carcinoma, given analysis in any biological or any non testis tissue sample.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

Given the lack of guidance in the specification as to expression analysis using fragments, complements, variants, and homologs of SEQ ID NO: 42 in any type of disorder, cancer in general or any specific cancers, as well as the unpredictability taught in the art with regard to CT antigen expression in general and HAGE (SEQ ID NO: 42) specifically, in both normal and cancerous tissues, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. The skilled artisan would first be required to determine if any fragment, complement, variant or homolog of SEQ ID NO: 42 could be used for diagnostic gene expression analysis in any disorder, cancer in general, or any specific cancer. Such experimentation would be replete with trial and error analysis because SEQ ID NO: 42 is a member of a family of helicases which contain conserved sequences. Such variants and homologs would be expected to be expressed in normal tissues. Given the fact that the specification provides no evidence that any fragment, complement, variant, or homolog of SEQ ID NO: 42 is diagnostic in hybridization analysis, the claims represent an invitation to experiment.

Additionally, the skilled artisan would be required to perform a large study of a wide range of tumor samples and normal tissues to determine if expression of SEQ ID NO: 42 was predictably diagnostic of any disorder, cancer in general, or any specific cancer. Such would require a large quantity of trial and error experimentation which the post filing date art teaches is unpredictable. Therefore, given the breadth of the claims and the nature of the invention, the lack of guidance in the specification, the state of the art, the unpredictability in art, the quantity of unpredictable trial and error experimentation, balanced only against the level of skill in the art, such experimentation is considered undue.

Conclusion

5. No claims are allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
6/24/04